Remarks:

The July 29, 2005 Official Action has been carefully considered. In view of the amendments submitted herewith and these remarks, favorable reconsideration and allowance of this application are respectfully requested.

At the outset, it is noted that a shortened statutory response period of three (3) months was set in the July 29, 2005 Official Action. The initial due date for response, therefore, was October 29, 2005. A petition for a three (3) month extension of the response period is presented with this amendment and request for reconsideration, which is being filed before the expiration of the three (3) month extension period, as January 29, 2006 fell on Sunday.

In the July 29, 2005 Official Action, the drawings were objected to because capitalization of panel letters shown in certain of the drawings does not match the Brief Descriptions of the Drawings (specification pages 26-28).

Turning to the substantive aspects of the July 29, 2005 Official Action, claims 29-31, 37-43 and 62-68 stand rejected as allegedly failing to comply with the written description requirement of 35 U.S.C. §112.

Claims 13-15, 29-35, 37-43 and 66-69 have been rejected for allegedly failing to comply with the enablement requirement of 35 U.S.C. §112, first paragraph. There are two (2) aspects to this ground of rejection. First, the examiner contends that the enablement provided by the specification does not warrant the present claim scope, in the case of claims 13-15, 29-35, 37-43 and 66-69. The examiner further contends in this regard that undue experimentation would be required to practice the subject matter claimed in claims 13-15, 41-43 and 66-68, which relate to the treatment of

Parkinson's Disease.

Claims 29, 30 and 37 have been further rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for the reasons of record, with respect to claim 29, and in view of the claim recitation "isolating and/or purifying" in claims 30 and 37.

Claims 1-3 and 5-12 have been rejected under 35 U.S.C. §103(a) as allegedly obvious over U.S. Patent 6,284,539 to Bowen et al. (hereinafter "the Bowen patent") in view of Takeshima et al., Neuroscience, 60(3): 809-23 (1994) (hereinafter "the Takeshima article").

The foregoing objection and rejections constitute all of the grounds set forth in the July 29, 2005 Official Action for refusing the present application.

In accordance with the present amendment, the Brief Description of the Drawings section of the specification has been amended so as to correspond to the drawing figures as originally filed. As a result of this amendment, it is believed that the drawing objection set forth in the July 29, 2005 Official Action has been overcome.

Given that claims 29-31, 37-43 and 62-68 are directed to methods of screening for receptors and factors obtained from Type 1 astrocytes of the ventral mesencephalon, the rejection of these claims for allegedly failing to comply with the written description requirement of 35 U.S.C. §112 is believed to be unfounded. Indeed, the examiner's argument in support of this rejection contains a number of factual inaccuracies. Nevertheless, purely in the interest of expediting prosecution and allowance of this application, claims 29-31, 37-43 and 62-68 are canceled in accordance with this amendment.

The rejection of claims 13-15, 29-35, 37-43 and

66-69 for allegedly failing to comply with the enablement requirement of 35 U.S.C. §112 is likewise flawed. The present specification provides more than ample guidance for those skilled in the art to carry out the screening methods claimed in claims 29-35, 37-40 and 69. As for claims 13-15, 41-43 and 66-68, the examiner mischaracterizes the claimed subject matter as "in vivo methods of treating Parkinson's disease....". Applicants again point out that the subject matter sought to be patented is as defined in the claims themselves, thus requiring a step of administration. The claims are not directed to "gene therapy" and all citations by the examiner that are directed to "gene therapy" are irrelevant. However, purely in the interest of expediting prosecution and allowance of the present application, these claims have been canceled in accordance with this amendment.

In view of the cancellation of claims 13-15, 29-35, 37-43 and 62-69, the aforementioned rejections of these claims based on 35 U.S.C. §112, first paragraph are rendered moot, as is the 35 U.S.C. §112, second paragraph rejection of claims 29, 30 and 37 based on alleged indefiniteness.

The cancellation of claims 13-15, 29-35, 37-43 and 62-69 should not be construed as indicative of applicants' concurrence or acquiescence in the various rejections of those claims set forth in the July 29, 2005 Official Action, or otherwise as an abandonment of applicants' efforts to secure patent protection on the subject matter of those claims. On the contrary, claims 13-15, 29-35, 37-43 and 62-69 are being canceled without prejudice to applicants' right and intention to file and prosecute one or more continuing applications directed to the subject matter of the canceled claims.

After entry of the present amendment, the only

rejection remaining to be addressed is the 35 U.S.C. §103(a) rejection of claims 1-3 and 5-12, based on the combined disclosures of the Bowen patent and the Takeshima article. For the reasons given hereinbelow, this rejection is respectfully traversed.

As noted by The Patent and Trademark Office Board of Appeals in Ex parte Wolters, 214 U.S.P.Q. 735 (Bd. Apps. 1979). The burden of establishing a prima facie case of obviousness falls upon the examiner. In determining whether a case of prima facie obviousness exists, it is necessary to ascertain whether or not the disclosures of the cited prior art references would appear to be sufficient to motivate one of ordinary skill in the art having the references before him or her to make the claimed substitution, combination or other modification. In re Lintner, 173 U.S.P.Q. 560 (C.C.P.A. 1972).

The examiner's argument that claims 1-3 and 5-12 are prima facie obvious in view of the combined disclosure of the Bowen patent and the Takeshima article is clearly invalid, as it is based on erroneous premises. Specifically, the examiner erroneously characterises the disclosure of the Takeshima article as reading on "co-culturing neural progenitor cells with Type 1 astrocytes of the mesencephalon and inducing a dopaminergic neuronal fate". Furthermore, the examiner incorrectly applies the actual disclosure of the Takeshima article as though it discloses features of the present claims which, if combined with features within the disclosure of the Bowen patent in the manner proposed, would lead to the present invention.

The examiner has overlooked the fact that the Takeshima article is concerned with promotion of survival of cells in primary culture that are already neuronal cells, whereas the present invention resides in the novel

and unobvious finding that neural stem cells or neural progenitor cells can be induced to adopt a dopaminergic neuronal fate by co-culturing with a Type 1 astrocyte of the ventral mesencephalon.

Page 22 of Takeshima et al states:

> "We conclude that in the primary culture studied, and under the experimental conditions used, the survival of dopaminergic neurons was independent of glia during the first nine days, and critically dependent on glia thereafter. The resurgence of growth of dopaminergic neurons after 10 days in vitro, and their subsequent selective survival in culture, suggest that confluent type-1 astrocytes produce factors that act selectively on the dopaminergic neuronal phenotype. The successful identification of these dopaminergic-specific, neurotrophic factors could lead to an increased understanding of the etiology of Parkinson's disease, and suggest new directions for therapeutic intervention. [emphasis added]"

The disclosure of the Takeshima article differs from the present invention in at least the following:

(1) The Takeshima article is concerned with an assay based on primary dopaminergic neurons, whereas the present invention acts on undifferentiated and immature stem cells. The Takashima article deals with the survival-promoting effects of type-1 astrocytes on primary cultures of the ventral mesencephalon already containing dopaminergic neurons (cultures from embryonic day 14). By contrast, the present invention employs immature, multipotent stem cells or progenitor cells,

that are (prior to treatment) not fated to acquire any specific phenotype and certainly not a dopaminergic phenotype. Furthermore, the cells may be derived from a completely different brain region, the cerebellum.

(2) In the work reported in the Takeshima article, astrocytes are employed as the source of neurotrophic factors, whereas in the present invention astrocytes are employed as the source of instructive factors. The Takashima article concludes that astrocytes produce neurotrophic factors, since the effects are on neuritogenesis and survival of cells that are already in the culture the beginning of the experiment and work in a selective manner. The present invention instead employs astrocytes as the source of instructive factors since they provide instruction to a multipotent stem cell to acquire an unexpected phenotype for a cerebellar stem cell: a dopaminergic phenotype. The results show that as a consequence of the instructive information, cells that were otherwise not fated to be any specific cell type (multipotent) acquire in a synchronous and exclusive manner (up to 90% of the cells) a neuronal phenotype of a dopaminergic type. Applicants believe that at the time they reported this finding, there were no data in the literature to suggest that astrocytes would produce anything else but survival neurotrophic factors. The findings are believed to have been the first to provide evidence for astrocytes being the source of instructive factors capable of inducing a neuronal-specific neurotransmitter phenotype in an undifferentiated multipotent stem cell. Similar findings were subsequently reported for hippocampal neurons by the group of Fred Gage, in Song et al., Nature (2002) 417(6884): 39-44 - copy attached). Note that the abstract of Song et al. reports: "[W]e discovered that adult astrocytes from hippocampus are capable of regulating neurogenesis by instructing the stem cells to

adopt a neuronal fate. This role in fate specification was unexpected....". The present invention has been thereafter widely accepted, but at the time it was first described there was very strong resistance to such an idea, because astrocytes are born relatively late during development and it was surprising that they would be the source of instructive signals. It is now known that cells in the adult brain with the appearance of astrocytes can serve multiple functions including working as stem cells themselves, and they can be not only the source of survival factors and nutrients (as classically accepted) but also the source of powerful instructive signals.

The present invention, as currently defined in claim 1, involving inducing a dopaminergic neuronal fate in a neural stem cell or neural progenitor cell by a method comprising expressing Nurr1 above basal levels within the cell and co-culturing the cell with a Type 1 astrocyte of the ventral mesencephalon, is both unique and non-obvious when considered in relation to the cited prior art.

It is quite apparent that the examiner has used applicants' disclosure as a guide for combining unrelated prior art teachings in an effort to make out a case of prima facie obviousness. Such hindsight reconstruction has long been held impermissible, since it is contrary to the standard of obviousness set forth in 35 U.S.C. §103, which requires a determination of whether the claimed subject matter as a whole would have been obvious at the time the invention was made, based on the state of the art as reflected in the cited references, and without benefit of applicants' disclosure. Neither of the references relied on by the examiner in support of the §103 rejection of claims 1-3 and 5-12 contains the slightest suggestion to use what is disclosed in one

reference in combination with what is disclosed in the other references. Cf. In re Avery, 186 U.S.P.Q. 161 (C.C.P.A. 1975). That being the case, it cannot reasonably be maintained that the disclosures of the Bowen patent and the Takeshima article fairly suggest doing what the applicants have done. Accordingly, the rejection of claims 1-3 and 5-12 under 35 U.S.C. §103 based on the combination of these two references is improper. Ex parte Stauber, 208 U.S.P.Q. 945 (Bd. Apps. 1980).

In summary, because the combined disclosures of the Bowen patent and Takeshima article fail to teach or suggest the claimed subject matter as whole, it necessarily follows that the prior art does not render applicants claims 1-3 and 5-12 prima facie obvious. Accordingly, the rejection of claims 1-3 and 5-12 under 35 U.S.C. §103(a) based on the combined disclosures of the Bowen patent and the Takeshima article is untenable and should be withdrawn.

In view of the present amendment and the foregoing remarks, it is respectfully urged that the objection and rejections set forth in the July 29, 2005 Official Action be withdrawn and that this application be passed to issue, and such action is earnestly solicited.

Respectfully submitted,
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Attachments:
- Copy of Song et al., Nature, 417(6884):39-44 (2002)